Gayle B. Thomas, MD; Gary N. Asher, MD, MPH; Anne Mounsey, MD
Department of Family Medicine, University of North Carolina at Chapel Hill

PURLs EDITOR
Bernard Ewigman, MD, MSPH
Department of Family Medicine, The University of Chicago

Finally, a way to relieve cancer-related fatigue

A 4-week course of American ginseng, taken while patients are undergoing radiation or chemotherapy, can reduce cancer-related fatigue.

PRACTICE CHANGER

Recommend American ginseng 1000 mg twice daily for 4 weeks to improve cancer-related fatigue for patients who are undergoing radiation or chemotherapy; no other treatment has been shown to be effective.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single well-done randomized controlled trial (RCT).

Barton DL, Liu H, Dakhil SR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst.* 2013;105:1230-1238.

ILLUSTRATIVE CASE

A 54-year-old woman is receiving chemotherapy for adenocarcinoma of the right breast (T2N1M0) and has persistent, disabling fatigue. She has been unable to work or care for her family since starting chemotherapy. She says she gets enough sleep and denies being depressed or in pain. Lab testing for anemia and thyroid dysfunction is negative.

Is there a safe and effective intervention that can reduce her fatigue?

Cancer-related fatigue is a common, distressing symptom that occurs in more than half of all patients undergoing chemotherapy and over two-thirds of those receiving radiation therapy.[2] For many cancer survivors, fatigue can persist for 5 to 10 years after treatment.[3] Because no treatments have been effective, many clinicians and patients accept it as inevitable. In RCTs, psychostimulants such as methylphenidate and antidepressants such as donepezil and paroxetine have not been found effective.[4-6] Dietary supplements such as coenzyme Q10 and L-Carnitine also have not been found effective in placebo-controlled trials.[7,8] The double-blind RCT reported on here looked at whether American ginseng might be effective in relieving cancer-related fatigue.

STUDY SUMMARY

Ginseng reduced fatigue after 8 weeks of treatment

There are 2 major species of ginseng—Asian and American—and they have varying amounts, strengths, and varieties of ginsenosides, which are the active ingredients. In this 8-week, double-blind RCT, Barton et al[1] randomized more than 300 patients from 40 US cancer facilities to receive either 1000 mg of American ginseng twice daily (in the morning and at noon) or matched placebo capsules. Patients were either currently receiving treatment for cancer or were posttreatment, but within 2 years of receiving a cancer diagnosis. All participants had experienced fatigue for at least a month that they rated as ≥4 or higher on a scale of 0 to 10. Patients with other causes of fatigue were excluded, as were those who had pain or insomnia rated ≥4 on a scale of 0 to 10, those with brain cancer or central nervous system (CNS) lymphoma, those taking systemic steroids or opioids, and those who were using, or had used, ginseng or other agents for fatigue.

Of the 364 randomized participants, 300 (147 ginseng patients, 153 placebo patients) remained in the study through the primary endpoint at 4 weeks, and 261 completed the entire 8-week study. There were no baseline differences between groups in demographic characteristics, time since cancer diagnosis, cancer type, current or prior treatment, and fatigue at baseline.

The primary outcome was a change in score on the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) at 4 weeks. Secondary outcomes included a change in MFSI-SF score at 8 weeks. The authors also conducted a subset analysis comparing ginseng vs placebo in just those patients currently undergoing cancer treatment vs those who had completed treatment. To make it easier to compare results, all scores were converted to a 100-point scale; higher scores indicated less fatigue. Adverse events were documented by patient self-report questionnaires and also by researchers who called or visited patients every other week.

While ginseng did not appear to significantly increase the change in fatigue scores over placebo at 4 weeks (14.4 vs 8.2; *P*=.07), fatigue scores at 8 weeks were significantly improved (20 vs 10.3; *P*=.003). Interestingly, though, there was a significant improvement in fatigue scores with ginseng at both 4 weeks (*P*=.02) and 8 weeks (*P*=.01) when researchers looked at only those patients who were currently receiving cancer treatment. On the other hand, those patients who were not currently undergoing treatment did not show a significant improvement at either time cutoff.

There was no statistically significant difference in adverse events between the ginseng and placebo groups over the 8-week study.

WHAT'S NEW

The first evidence-based therapy for cancer-related fatigue

We now have good evidence that American ginseng 1000 mg twice daily is safe and effective for ameliorating cancer-related fatigue. Before this study, no other effective treatments had been identified.

CAVEATS

Ginseng may not help patients who've finished cancer treatment

In this study, ginseng did not improve fatigue at 4 weeks, which was the primary outcome, although benefits were noted after 8 weeks of treatment. Interestingly, though, participants who were receiving radiation and/or chemotherapy during the study experienced significant improvements at 4 and 8 weeks, while those with previous (but not current) treatment did not significantly improve at either time point.

It may be that ginseng works best to ameliorate cancer-related fatigue in patients simultaneously receiving cancer treatment, but not in those who have completed treatment. The findings also suggest that patients who have completed treatment may wish to try ginseng for longer than 8 weeks to see if it offers any benefit.

Because this study excluded patients with brain cancer, CNS lymphoma, moderate to severe pain, or insomnia and those taking steroids, it is not known if ginseng would help them.

In one study, a low-dose methanolic extract of American ginseng caused a breast cancer cell line to proliferate; however, it was later discovered that this extract had been contaminated with *Fusarium* fungi containing zearalenone, which has strong estrogenic activity.[9,10] However, higher doses of a similar methanolic extract, as well as other water-based extracts, have reduced proliferation of breast cancer cells.[11]

Proceed carefully if a patient is taking warfarin. Coadministration of ginseng and warfarin may reduce both warfarin concentrations and a patient's international normalized ratio (INR).[12] Therefore, carefully monitor INR in patients concurrently taking ginseng and warfarin. Furthermore, ginseng may lower blood glucose in patients with diabetes, so carefully monitor blood glucose in these patients when initiating or discontinuing ginseng.[13]

CHALLENGES TO IMPLEMENTATION

With ginseng, it's hard to know exactly what you're getting

Regulating dietary supplements has been a challenge for the US Food and Drug Administration, especially verifying ingredients

Coadministration of ginseng and warfarin may reduce both warfarin concentrations and a patient's INR.

and potency. Although ginseng commonly is adulterated, much of the adulteration occurs with the Asian species (*Panax ginseng*) rather than the American species (*Panax quinquefolius*) used in this study.[10] Physicians who want to recommend ginseng for cancer-related fatigue should advise patients to use American ginseng root products produced in the United States. Additionally, ginseng products should contain at least 3% ginsenosides to match the dose used in this study. JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

Advise patients to obtain American ginseng products that contain at least 3% ginsenosides.

References

1. Barton DL, Liu H, Dakhil SR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst*. 2013;105:1230-1238.
2. Hofman M, Ryan JL, Figueroa-Moseley CD, et al. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007;12 suppl 1:4-10.
3. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. *Cancer*. 2006;106:751-758.
4. Moraska AR, Sood A, Dakhil SR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol*. 2010;28:3673-3679.
5. Bruera E, El Osta B, Valero V, et al. Donepezil for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol*. 2007;25:3475-3481.
6. Morrow GR, Hickok JT, Roscoe JA, et al; University of Rochester Cancer Center Community Clinical Oncology Program. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol*. 2003;21:4635-4641.
7. Lesser GJ, Case D, Stark N, et al; Wake Forest University Community Clinical Oncology Program Research Base. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. *J Support Oncol*. 2013;11:31-42.
8. Cruciani RA, Zhang JJ, Manola J, et al. L-carnitine supplementation for the management of fatigue in patients with cancer: an Eastern cooperative oncology group phase III, randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2012;30:3864-3869.
9. Duda RB, Zhong Y, Navas V, et al. American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 breast cancer cell growth. *J Surg Oncol*. 1999;72:230-239.
10. Upton, R (ed). American ginseng root panax quinquefolius, standards of analysis, quality control, and therapeutics. Scotts Valley, CA: American Herbal Pharmacopoeia; 2012.
11. King ML, Adler SR, Murphy LL. Extraction-dependent effects of American ginseng (Panax quinquefolium) on human breast cancer cell proliferation and estrogen receptor activation. *Integr Cancer Ther*. 2006;5:236-243.
12. Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med*. 2004;141:23-27.
13. Vuksan V, Stavro MP, Sievenpiper JL, et al. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes Care*. 2000;23:1221-1226.